Epidemiology, clinical features and diagnosis of neuropathic pain

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Chapter 1

1.1. Epidemiology

A considerable proportion of the western population suffers from chronic pain. Estimates on prevalence figures diverge and range from 2 to 55,2%, depending on the criteria that the researchers set for their definition of chronic pain *[Crombie et al., 1994; Verhaak et al., 1998; Elliot et al., 1999; Van Cranenburgh, 2002; Picavet & Schouten, 2003; Harstall et al., 2003]*. Usually, pain is considered chronic if there is no obvious injury *[Macres et al., 1999]* or when it persists for months and years - beyond the normal time of healing *[Bonica, 1953; Turk & Okifuji, 2002, Harstall et al., 2003 (IASP)]*. Others consider a chronic pain syndrome to be present when a patient's coping strategies fail *[Vissers, 2006]*. Long-lasting pain due to chronic inflammatory diseases (*e.g.* rheumatoid arthritis) or cancer should not be called chronic pain, as long-lasting nociception is present. There is no single, uniform definition of when pain is chronic.

About 25% of these patients with chronic pain will have neuropathic pain *[Bowsher, 1991]*. It is estimated that 1,5% - 3% of the population suffers from neuropathic pain *[Smith and Chong, 2000; Carter et al., 2001; Chong et al., 2003; Gilron et al., 2006]*. However, chronic neuropathic pain is likely to be much more common than has generally been appreciated *[Dworkin, 2002]*. Disorders such as degenerative diseases, cancer, low back pain, traumatic injury may all contain considerable neuropathic components *[Jensen and Baron, 2003; Chong, 2003]*. This underestimated prevalence of neuropathic pain is illustrated in a study by Torrance et al., who measured a prevalence of "pain of predominantly neuropathic origin" of 8% *[Torrance et al., 2006]*. In comparison; the prevalence of other frequently occurring diseases such as diabetes mellitus type 2 is estimated to be 3% *[Ubink-Veltmaat et al., 2003]*.

The economic costs of neuropathic pain are considerable; in the US the annual costs of neuropathic pain are estimated to amount to $40 billion *[Gilron et al., 2006]*. Patients with neuropathic pain have been found to generate a 3-fold higher health care costs than matched control subjects *[Berger et al., 2004]*.

1.2. Neuropathic pain

The International Association for the Study of Pain (IASP) defines neuropathic pain as pain initiated or caused by a primary lesion or dysfunction in the nervous system *[Merskey and Bogduk, 1994]*.

Neuropathic pain differs from the more familiar nociceptive pain, as the latter is initiated by sensory nociceptor fibres following imminent or actual tissue damage *[Woolf and Salter, 2000]*. Nociceptive pain has a protective role; it elicits reflex and behavioural responses that prevent the damage from escalating *[Woolf and Mannion, 1999]*. Nociceptive pain is generally well localised, it usually responds sufficiently to classic analgesic drugs and subsides with healing or removal of the noxious stimulus *[Stannard and Booth, 1998; Chong et al., 2003]*.

The origin of neuropathic pain lies within the nervous system itself, rather than in the activation of peripheral nociceptors. Examples of neuropathic pain syndromes include: phantom limb pain, diabetic neuropathy, postherpetic neuralgia, trigeminal neuralgia and thalamic pain. However, the distinction between neuropathic pain and nociceptive pain is not as clear-cut as it may seem. For example, radicular pain is the consequence of both nociception and

irritation of the involved dorsal root. This form of neuropathic pain is also called nociceptive neuropathic pain, which is defined by the IASP as pain initiated or caused by activation of the nervi nervorum (of the nerve trunk) by local ongoing tissue damage *[Merskey and Bogduk, 1994; Dellemijn, 1997]*. Another form of neuropathic pain is deafferentation pain, which is non-nociceptive in nature and results from distorted somatosensory information and sensitisation of pain modulating systems within the peripheral and central nervous system *[Dellemijn, 1997; Woolf and Mannion, 1999; Jensen et al., 2003]*.

Table 1. Common types of neuropathic pain

Peripheral neuropathic pain

- Acute and chronic inflammatory demyelinating polyradiculopathy
- Alcoholic polyneuropathy
- Chemotherapy-induced polyneuropathy
- Complex Regional Pain Syndrome (CRPS)
- Entrapment neuropathies (*e.g.*, carpal tunnel syndrome)
- HIV sensory neuropathy
- Iatrogenic neuralgias (*e.g.*, postmastectomy pain or postthoracotomy pain)
- Idiopathic sensory neuropathy
- Nerve compression or infiltration by tumour
- Nutritional deficiency-related neuropathies
- Painful diabetic neuropathy
- Phantom limb pain
- Postherpetic neuralgia
- Post radiation plexopathy
- Posttraumatic neuralgias
- Radiculopathy (cervical, thoracic or lumbosacral)
- Toxic exposure-related neuropathies
- Tic douloureux (trigeminal neuralgia)

Central neuropathic pain

- Compressive myelopathy from spinal stenosis
- HIV myelopathy
- Multiple sclerosis-related pain
- Parkinson disease-related pain
- Post ischemic myelopathy
- Post radiation myelopathy
- Post stroke pain
- Posttraumatic spinal cord injury pain
- Syringomyelia

Table 1. Classification of neuropathic pain based on the localisation of aetiology, *i.e.*, peripheral or central. Reprinted from Dworkin et al., Advances in neuropathic pain. Diagnosis, mechanisms, and treatment recommendations. Archives of Neurology Vol60:p1524-1534.

A third, perhaps even more complex form of neuropathic pain is sympathetically maintained pain. This type of pain is characterised by the involvement of the autonomous, sympathetic nervous system and includes Complex Regional Pain Syndrome (CRPS) types 1 and 2 *[Bridges et al., 2001; Campbell et al., 2006].*

According to the IASP-definition, disorders that are characterised by pain due to a *dysfunction* of the nervous system can also be considered as neuropathic pain syndromes. This would imply that disorders such as fibromyalgia, chronic low back pain and whiplash associated disorder (WAD) are neuropathic pain syndromes. Indeed, there is compelling evidence from recent research that shows spinal cord hyperactivity as the major cause for the pain in patients with these chronic pain syndromes *[Price et al., 2002; Banic et al., 2004; Giesecke et al., 2004; O'Neill et al., 2007]*. However, the term neuropathic pain is mostly reserved for disorders with a lesion of the nervous system and in which positive and/or negative sensory symptoms, such as anaesthesia, hyperalgesia and allodynia, can be demonstrated *[Hansson, 2002; Jensen and Baron, 2003; Chong et al., 2003]*.

Treatment options for neuropathic pain - as opposed to nociceptive pain - are poor. Whereas more than 90% of patients with nociceptive pain can achieve adequate pain relief, it is estimated that the number of patients with neuropathic pain needed to treat (NNT) before one patient experiences a 50% improvement is, at best, between 2,5 and 4. This means that (with monotherapy) the chance of adequate pain relief for patients with neuropathic pain is only one in three *[McQuay and Moore 1998 ; Irving, 2005]*. It needs to be considered that a 50% pain relief is usually considered satisfactory *[McQuay and Moore, 1998; Finnerup et al., 2007]*. Farrar et al. (2001) demonstrated that patients may also consider a 30% pain reduction to be significant. With a lower standard the NNT would obviously also be lower. Furthermore, many patients with neuropathic pain are treated inadequately, *i.e.* with classical analgesic drugs such as NSAIDs, instead of antiepileptic drugs and tricyclic antidepressants, which are more effective against neuropathic pain *[Berger et al., 2004]*. This suboptimal treatment of neuropathic pain is also our experience and may very well be due to both the under-diagnosing of neuropathic pain and insufficient knowledge of treatment options by many physicians.

All in all, neuropathic pain poses a considerable challenge for physicians in the field of pain management; not only to recognise neuropathic pain, but also to translate its symptoms into postulated underlying pathophysiological mechanisms, in order to apply adequate therapeutic intervention(s).

1.3. Clinical features of neuropathic pain and diagnostic workup

Assessment of the patient with suspected neuropathic pain should focus on ruling out treatable conditions (*e.g.*, spinal cord compression, neoplasm), confirming the diagnosis of neuropathic pain and identifying clinical features (*e.g.*, insomnia, autonomic neuropathy) that might help individualise treatment *[Gilron et al., 2006]*.

The first step in the diagnostic workup is the meticulous collection of the medical history, followed by a comprehensive physical and neurological examination *[Jensen and Baron, 2003; Chong et al., 2003; Irving, 2005]*. The outcome of such bedside examination is generally suf-

ficient for the establishment of an adequate diagnosis. Upon indication, additional neurophysiological testing may be performed, such as quantitative sensory testing (QST), electrophysiological testing and neuroimaging *[Hansson, 2002]*.

Whereas nociceptive pain is usually finite, well-localised and subsides upon removal of the nociceptive source, neuropathic pain may exist independently from any causal stimulus. Medical history provides insight in the onset, duration, quality, location and efficacy of previous therapy *[Hansson, 2002; Jensen and Baron, 2003; Chong et al., 2003; Vissers, 2006]*. Both temporal and spatial aspects of the pain should be explored. Temporal aspects of pain - constant vs. intermittent/paroxysmal pain – can be indicative for specific diagnoses, *e.g.* trigeminal neuralgia. Preferably, the spatial aspects of the pain should be clarified further by a pain drawing made by the patient, as the distribution of pain may match affected nerves or dermatomes. Neuropathic pain is often described in terms of 'shooting', 'lancinating', 'burning', or even more narrative, such as: 'it feels as ants crawling up my leg'. Spontaneous pain can be constant, intermittent or both *[Dworkin et al., 2003]*. A patient who was shot in his left arm during the American Civil War in 1862 described his neuropathic pain to Silas Weir Mitchell, a neurologist who treated wounded soldiers with injuries to peripheral nerves: 'it is as if a rough bar of iron were thrust to and fro through the knuckles, a red-hot iron placed at the junction of the palm and thenar eminence, with a heavy weight on it, and the skin was being rasped off my finger ends' *[Mitchell, 1872]*. Although vivid - and sometimes strange - denominators are used to illustrate their neuropathic pain, patients with both nociceptive and neuropathic pain demonstrate considerable overlap in the use of pain descriptors *[Hansson, 2002; Jensen and Baron, 2003]*.

Inadequate response to classic analgesic drugs (*e.g.* NSAIDs) may point towards a neuropathic mechanism of the pain instead of nociception. Furthermore, assessment tools, such as the Neuropathic Pain Scale and the Leeds Assessment of Neuropathic Symptoms and Signs Pain Scale, have been introduced recently and may facilitate diagnosing neuropathic pain *[Bennett et al., 2005; Bennett et al., 2007; Rog et al., 2007]*. Validation of these pain scales is still in progress.

As chronic (neuropathic) pain leads to many psychosocial and physical impairments, a biopsychosocial model should be used to integrate mechanical, pathophysiological, psychological and social-contextual variables that may have caused and/or perpetuated the pain. Symptoms as insomnia, anorexia, anxiety, depression, physical inactivity and a diminished quality of life should be recognised and addressed accordingly *[Turk and Okifuji, 2002; Irving, 2005]*.

Physical and neurological examination should be performed to investigate the presence of treatable conditions, and to determine the presence and extent of sensory abnormalities, *i.e.* positive and/or negative symptoms *[Gilron et al., 2006]*. Signs of nociceptive neuropathic pain, such as a positive Lasègue (straight leg raising test) in the case of dorsal root compression, or the presence of a dermatomal rash and shingles in the case of acute Herpes Zoster, should yield further clues for an accurate diagnosis *[Dellemijn, 1997]*. A tentative diagnosis is the guide to specific sensory examination *[Hansson, 2002]*.

Careful sensory examination should include the use of simple tools as a pin, a (paint) brush,

ice, and a cold and warm metal roller. Exploring the entire spectrum of fibres is crucial, since sensory disturbances may be confined to specific modalities. Assessment should be performed in the area with maximal pain using the contralateral, unaffected skin as control *[Baron, 2006]*. In clinical practice, the response can be simply graded as: normal, decreased/increased or absent *[Jensen and Baron, 2003]*.
The area in which sensory dysfunction is found, should be mapped to investigate whether it matches the innervation territory of a nervous structure. It should be taken into account that extraterritorial spread of pain, a symptom of central sensitisation, can be found frequently.
Negative symptoms are the result of sensory impairment, *e.g.* in the case of anaesthesia dolorosa, a neuropathic pain syndrome characterised by pain in an area which is anaesthetic *[Merskey and Bogduk, 1994]*. Partial nociceptive deafferentation may lead to a state of painful hypoalgesia *[Baumgärtner et al., 2002]*.
Most of the positive sensory symptoms (hyperesthesia) will be painful in nature and can be subdivided into hyperalgesia, allodynia and hyperpathia (see table 2). These symptoms are also called stimulus-evoked pain *[Woolf and Mannion, 1999]*. Whereas hyperalgesia and allodynia are characterised by abnormal sensation following the application of a stimulus, hyperpathia entails increasing pain upon repetitive stimulation (temporal summation).

Table 2. IASP definitions of pain and its concomitant symptoms

Allodynia	Pain due to a stimulus which does not normally provoke pain.
Hyperalgesia	An increased response to a stimulus which is normally painful.
Hyperpathia	A painful syndrome characterised by an abnormally painful reaction to a stimulus, especially a repetitive stimulus, as well as an increased threshold.
Neuropathic pain	Pain initiated or caused by a primary lesion or dysfunction in the nervous system.
Pain	An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage.

Table 2. IASP definitions of pain and its concomitant symptoms that are relevant for this thesis. For a more extensive overview of all recent definitions, we refer to the IASP website; www.iasp-pain.org.

Autonomic signs may be a direct consequence of nerve injury or a (supra-)spinal reflex to nociceptive input *[Bennett and Ochoa, 1991]*. Vasodilatation results from complete neurotomy in the early phase due to the loss of vasoconstrictor tone, followed by later vasoconstriction due to denervation hypersensitivity of blood vessels *[Hansson, 2002]*. Other autonomic signs include for example abnormal sweating or trophic changes of the skin *[Gilron et al.,*

2006]. Motor dysfunction, such as tremor and weakness, in the absence of damage of the motor system is either a somatosensory reflex, protective behaviour, or a psychologically conditioned overlay *[Hansson, 2002]*.
Multiple combinations of positive and negative symptoms are possible in neuropathic pain syndromes; no common pathological somatosensory pattern has been identified in neuropathic pain states. Data from basic research demonstrate that neuropathic pain may be the consequence of various pathophysiological mechanisms. Different mechanisms may coexist in a single patient and change over time *[Hansson, 2002]*. Dissecting these mechanisms is probably not possible in clinical practice *[Jensen and Baron, 2003]*.

Table 3. Characteristics of neuropathic pain

- There is usually no tissue damage that is responsible for the persistence of the pain (except in nociceptive neuropathic pain syndromes, such as compression neuropathies)
- Sensory aberrations co-occur with the pain, i.e. hypoesthesia, allodynia and / or hyperalgesia. There is increased summation upon repetitive stimuli
- The location of the pain is projected and does not match the source of the pain, *e.g.* neuropathic pain resulting from a herniated lumbar disc is located in the leg rather than the back
- The nature of the pain is frequently strange, *e.g.* crawling ants, or a red hot poke that is rubbed in the flesh
- The location of the pain tends to expand over time
- Response to classic analgesic is often poor

Table 3. Characteristics of neuropathic pain. Based on Van Cranenburgh (2002), with permission of Reed Business (Elsevier gezondheidszorg).

Upon indication, additional testing with neurophysiological and neuroimaging techniques may be performed to confirm or reject tentative diagnoses. When allodynia and/or hyperalgesia are present, these phenomena can be quantified by means of psychophysical quantitative sensory testing (QST). QST can be employed for further exploration of (subtle) somatosensory aberrations and results of QST can be used to evaluate treatment outcome more objectively *[Edwards et al., 2005; Keizer et al., 2007]*. For more details on the basic principles of QST, see chapter 3.

1.4. Conclusions

Chronic neuropathic pain is a disabling disease of the nervous system that affects all aspects of a patient's functioning; physical, emotional and social-contextual. Management of neuropathic pain poses a significant challenge for doctors and researchers, since treatment options are frequently insufficient to achieve adequate pain relief. Furthermore, neuropathic pain is a demanding burden on healthcare resources and generates considerable disability and related

costs, which will probably increase even more in the future. Nowadays, prevalence figures of neuropathic pain have been estimated to range from 1,5 – to 8% of the population.
Neuropathic pain is characterised by spontaneous pain as well as stimulus-evoked pain. Pain following light stimulation of the affected skin (allodynia) is a highly disabling symptom. Since allodynia is stimulus-evoked, it will elicit reflex and behavioural responses, compelling the patient's attention constantly.
Although advocated by many researchers working in the field of pain, a mechanism-based classification of neuropathic pain is not possible as yet. Multiple pathophysiological mechanisms underlie neuropathic pain; different mechanisms co-exist in a single patient and may change over time. Moreover, current diagnostic tools are too crude to dissect pathophysiological mechanisms. This attractive mechanism-based approach, however, may yield some clues for treatment; *e.g.* the presence of allodynia suggests central sensitisation, whereas autonomous symptoms point to the involvement of the sympathetic nervous system.
The first step towards well-considered therapy is meticulous history taking and comprehensive physical and neurological examination. Assessment of the patient with suspected neuropathic pain should focus on ruling out treatable conditions (*e.g.*, spinal cord compression, neoplasm), confirming the diagnosis of neuropathic pain and identifying clinical features *(e.g.*, insomnia, autonomic neuropathy) that might help individualise treatment.
Medical history provides insight in the onset, duration, quality, location and efficacy of previous therapy. Both temporal and spatial aspects of the pain should be explored. Efficacy of previously used medication must be considered. Symptoms as insomnia, anorexia, anxiety, depression, physical inactivity and a diminished quality of life should be recognised and addressed accordingly.
Physical and neurological examination should be performed to investigate the presence of treatable conditions, and to determine the presence and extent of sensory abnormalities, *i.e.* positive and/or negative symptoms. Careful sensory examination should include the use of simple tools as a pin, a (paint) brush, ice, and a cold and warm metal roller. The area in which sensory dysfunction is found, should be mapped to investigate whether it matches the innervation territory of a nervous structure. Autonomous signs and motor dysfunction should be detected, since these phenomena can be frequently observed in patients with neuropathic pain syndromes.
Upon indication, additional testing with neurophysiological and neuroimaging techniques may be performed to confirm or reject tentative diagnoses. Quantitative Sensory Testing (QST) can be employed for further exploration of (subtle) somatosensory aberrations.

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